Faslodex

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/08/2022		PL	
II/0073	Update of the RMP version 13 for fulvestrant to remove the additional risk minimisation measures for important identified risks and reclassifiy safety	10/06/2021	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	concerns based on Good Pharmacovigilance Practices (GVP) module V, risk management systems (revision 2) guidelines as requested by PRAC as a part of PRAC PSUR assessment report, procedure number EMEA/H/C/PSUSA/00001489/202004 covering the period 26/04/2017 to 25/04/2020. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/1489/ 202004	Periodic Safety Update EU Single assessment - fulvestrant	14/01/2021	n/a		PRAC Recommendation - maintenance
IB/0072/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	30/11/2020	n/a		
IA/0071/G	This was an application for a group of variations.	10/11/2020	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0069	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	28/05/2020	n/a		
II/0068	Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information based on the results from study Phase 3 Study A5481023 (PALOMA-3) a randomized controlled study of fulvestrant and palbociclib combination. In addition, the MAH took the opportunity to make a number of editorial changes to the PI to comply with the new QRD template v10.1 and the addition of the respective strength and pharmaceutical form to the corresponding Marketing Authorisation Number. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/04/2020	27/10/2020	SmPC, Annex II and Labelling	After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (60% of randomised patients). A 6.9-month difference in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed; this result was not statistically significant at the prespecified significance level of 0.0235 (1-sided). In the placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib and other CDK inhibitors as post-progression subsequent treatments. The ADR frequencies for fulvestrant combination therapy with palbociclib have been updated based on the new data cut-off. For more information, please refer to the Summary of Product Characteristics.
II/0067	To update the information on women of childbearing potential in section 4.6 of the SmPC following an review of non-clinical data, clinical pharmacology simulation/modelling data, supporting documentation and safety data; the Package Leaflet is updated	07/11/2019	27/10/2020	SmPC, Annex II and PL	Patients of childbearing potential should use effective contraception during treatment with Faslodex and for 2 years after the last dose.

	accordingly. In addition, the MAH has taken the opportunity to correct a minor mistake in the address of one of the manufacturers responsible for batch release in Annex II and PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0066/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	02/04/2019	01/08/2019	Annex II and PL	
IB/0065	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	25/02/2019	n/a		
IB/0064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/09/2018	01/08/2019	SmPC and PL	
T/0063	Transfer of Marketing Authorisation	27/02/2018	21/03/2018	SmPC, Labelling and PL	

PSUSA/1489/ 201704	Periodic Safety Update EU Single assessment - fulvestrant	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0059	Extension of Indication to include the use of Faslodex in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy; in pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist for Faslodex. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.3, 6.1, 6.5 and 6.6 of the SmPC are updated to update the safety and efficacy information. The Package Leaflet is updated in accordance. RMP version 12 was included in the application. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	12/10/2017	10/11/2017	SmPC and PL	Please refer to the Scientific Discussion Faslodex H-0540-II-59-AR
IAIN/0062	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/09/2017	10/11/2017	SmPC and PL	
II/0057	Extension of indication to include the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women who have not been previously treated with endocrine therapy. As a consequence, sections 4.1, 4.8, 4.9,	22/06/2017	25/07/2017	SmPC, Annex II and PL	To support the extension of indication in endocrine naïve patients, a supportive Phase 2 study D6995C00006 (FIRST) and a pivotal Phase 3 study D699BC00001 (FALCON) were submitted. Sections 4.1, 4.8, 4.9 and 5.1 of the SmPC are updated in

	and 5.1 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes in the SmPC. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				order to update the safety and efficacy information. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor modifications in the SmPC.
IB/0058/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/01/2017	n/a		
II/0055	Update of sections 4.2, 4.4, 4.8 and 6.6 of the SmPC in order to add precautionary language regarding the method of administration due to the proximity of the underlying sciatic nerve. In addition, the MAH update section 4.5 of the SmPC to include a warning of possible falsely elevated levels of estradiol in the use antibody based-estradiol assays in patients taking fulvestrant. The Package Leaflet and Labelling are updated accordingly.	21/07/2016	22/05/2017	SmPC, Labelling and PL	Following an analysis on safety data from clinical trials and post-marketed use, the MAH is updating sections 4.2, 4.4, 4.8 and 6.6 of the SmPC in order to add precautionary language regarding the method of administration due to the proximity of the underlying sciatic nerve. In addition, the MAH updates section 4.5 of the SmPC to include a warning of possible falsely elevated levels of estradiol in the use antibody based-estradiol assays in patients taking fulvestrant. The Package Leaflet and Labelling are updated accordingly.

	In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC in accordance with the latest QRD template and update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0056	A.1 - Administrative change - Change in the name and/or address of the MAH	24/06/2016	22/05/2017	SmPC, Labelling and PL	
IB/0054/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.2.e - Change in test procedure for AS or	29/04/2016	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
IA/0053/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	10/12/2015	n/a		
IG/0633	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	09/12/2015	n/a		
IAIN/0051	C.I.z - Changes (Safety/Efficacy) of Human and	11/09/2015	02/03/2016	SmPC, Annex	

	Veterinary Medicinal Products - Other variation			II and PL	
IB/0049	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/04/2015	n/a		
II/0047	Update of section 4.8 of the SmPC in order to add 'reduced platelet count' as an uncommon ADR. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make editorial changes to sections 4.8 and 5.2 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	02/03/2016	SmPC and PL	N/A
II/0046	B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	18/12/2014	n/a		
PSUV/0044	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
II/0042/G	This was an application for a group of variations. B.II.b.1 f) - Addition of Vetter Pharma-Fertigung GmbH & Co KG, Eisenbahnstrasse 2-4, Langenargen, Germany as an additional site for finished product manufacture (compounding and syringe filling).	20/11/2014	n/a		

	B.II.b.3 b) - Changes to the manufacturing process as a result of the new manufacturing site at Langenargen. B.II.d.2 a) - Increase to the sampling of the sterility testing at Langenargen. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IA/0045	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	08/10/2014	n/a		
IB/0043	B.I.d.1.a.4 - Stability of AS - Change in the re-test	11/06/2014	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
IG/0402	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	27/02/2014	n/a		
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/09/2013	18/12/2013	PL	
IA/0039/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	12/04/2013	n/a		

	procedure				
IG/0273	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/02/2013	n/a		
II/0036	The MAH proposed the update of section 5.1 of the SmPC to include the final overall survival data from Study D6997C00002 (CONFIRM) further to the assessment of FUM021. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.2 and to implement minor editorial changes. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	17/01/2013	18/12/2013	SmPC and Annex II	In this variation, section 5.1 of the SmPC has been updated in order to include final overall survival data from Study D6997C00002 (CONFIRM) further to the assessment of FUM021. At 75% maturity the study showed that fulvestrant 500 mg improved overall survival when compared with fulvestrant 250 mg (HR=0.81, 95% CI: 0.69 to 0.96, median 26.4 versus 22.3 months, respectively, p=0.016).
IB/0037	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	14/12/2012	18/12/2013	SmPC, Labelling and PL	
IAIN/0035	B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	01/03/2012	n/a		
II/0034	Update of section 4.8 of the SmPC to add new	19/01/2012	17/02/2012	SmPC, Annex	The review of the clinical safety database of Faslodex

	hepatobiliary disorders following a safety database research performed by the MAH. Section 4 of the package leaflet was proposed to be updated accordingly. Furthermore, the MAH took this opportunity to update the list of local representatives in the PL and to bring the PI in line with the latest QRD template (version 8.1, October 2011). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II, Labelling and PL	identified that elevated bilirubin, elevated gamma GT, hepatitis and hepatic failure were found in patients receiving Faslodex, but a possible causal association between these disorders and Faslodex remains unclear. Therefore section 4.8 of the SmPC has been updated to include the new hepatobiliary disorders.
II/0033	Update of section 5.3 of the SmPC to include safety information further to the assessment of the two-year mouse carcinogenicity study 0118CM (FUM 002). C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation	19/01/2012	17/02/2012	SmPC	Results from the two-year mouse carcinogenicity study 0118CM suggest that the findings, both neoplastic and non-neoplastic, seem related to the pharmacology of fulvestrant. Therefore, section 5.3 of the SmPC has been updated to reflect the increased incidence of ovarian sex cord stromal tumours (both benign and malignant) observed in the study at doses of 150 and 500 mg/kg/day. At the no-effect level for these findings, systemic exposure levels (AUC) were, in rats (based on data from previously reported studies), approximately 1.5 fold the expected human exposure levels in females and 0.8 fold in males, and in mice, approximately 0.8 fold the expected human exposure levels in both males and females. Induction of such tumours is consistent with pharmacology-related endocrine feedback alterations in gonadotropin levels caused by anti-estrogens in cycling animals. Therefore these findings are not considered to be relevant to the use of fulvestrant in postmenopausal women with advanced

					breast cancer.
II/0032/G	This was an application for a group of variations. - addition of 2 new manufacturing sites for the active substance B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions	19/01/2012	19/01/2012		
IG/0124/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	18/11/2011	n/a		
IA/0029/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits	18/11/2011	n/a		

	applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
II/0025	Update of sections 4.2, 4.4, 5.1 and 5.2 the SmPC based on paediatric data from Study D6992C0044 further to the assessment of the paediatric Article 46 follow up measure (P46 022). In addition Annex II has been updated to reflect the latest Risk Management Plan version number. Furthermore the MAH took the opportunity to update the local representative contact details in the package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	27/07/2011	SmPC, Annex II and PL	In this variation the SmPC has been updated with data from the paediatric study D6992C0044 in girls with Progressive Precocious Puberty associated with McCune Albright Syndrome (MAS) further to the assessment of the paediatric Article 46 follow up measure (P46 022). Faslodex remains not recommended for the use in children and adolescents as safety and efficacy have not been established, therefore no recommendations on posology can be made. The study showed a reduction in the frequency of vaginal bleeding and a reduction in the rate of bone age advancement. The steady-state trough concentrations of fulvestrant in children in this study were consistent with those in adults.
IB/0026	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	27/06/2011	n/a		
IB/0027	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	25/05/2011	n/a		
IA/0028/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement	19/05/2011	n/a		

	or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
IG/0035	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	07/01/2011	n/a	Annex II	
II/0018	Section 5.1 of the SmPC has been updated to include information on patients who have failed on prior anti-estrogen and aromatase inhibitor therapy. Moreover results relating to the mechanism of action, effects on bone and postmenopausal endometrium have also been included. In addition, section 4.8 of the SmPC has been updated to include bleeding at the injection site and information on arteritis in dogs has been included in section 5.3 of the SmPC. The Package Leaflet has been updated accordingly. Furthermore changes were made to the SmPC, labelling and Package Leaflet to bring them in line with the current QRD template and the list of local representatives in the Package Leaflet has been revised to amend contact details for the	23/09/2010	25/10/2010	SmPC, Annex II, Labelling and PL	In this application, the MAH re-evaluated data from a previously submitted pivotal study: CONFIRM, as well as supportive studies NEWEST, FINDER1 and FINDER2, to support an extension of indication to include data on patients who have failed on aromatase inhibitor therapy. Further to the assessment of the submitted data, the CHMP considered that efficacy data to support an extension of indication in this patient population was insufficient. However the CHMP considered acceptable to include relevant data on patients who have failed on prior anti estrogen and aromatase inhibitor therapy by subgroup in section 5.1 of the SmPC as the information can be helpful for the prescriber. Data from study NEWEST relating to mechanism of action, effects on bone and postmenopausal endometrium have also been included in section 5.1 of the SmPC. In addition section 4.8 of the SmPC has been updated to include bleeding at the injection site as an adverse

	representative of Czech Republic. Finally Annex II has been updated in order to reflect the latest version of the RMP agreed. Extension of Indication				reaction. Furthermore further to a re-analysis of the toxicological studies, section 5.3 of the SmPC has been updated to include information on arteritis in dogs. Please refer to Scientific Discussion Faslodex-H-C-540-II-18.
IB/0022	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	09/04/2010	09/04/2010	SmPC, Labelling and PL	
IA/0024	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	09/04/2010	n/a		
IA/0023	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/04/2010	n/a		
IA/0021	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	31/03/2010	n/a		
IA/0019	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	24/03/2010	n/a		
IA/0020	B.II.d.2.a - Change in test procedure for the finished	23/03/2010	n/a		

	product - Minor changes to an approved test procedure				
II/0017	Change in the dose regimen from 250mg to 500mg, based on data from the CONFIRM study (previously assessed in FUM 005). As a consequence, sections 4.2, 4.7, 4.8, 5.1 and 5.2 of the SPC have been updated. Further, sections 6.5 and 6.6 have been updated for increased clarity. Section 4.6 has also been revised to include recommendations during lactation. The Package Leaflet has been updated accordingly. In addition, the MAH takes the opportunity to make minor editorial changes to the SPC, Labelling and Package Leaflet, including an update of the contact details of the Slovenian local representative in the Package Leaflet. Furthermore, Annex II has been updated in order to include the version numbers for the Pharmacovigilance System and the Risk Management Plan, as per the latest QRD template. Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/01/2010	15/03/2010	SmPC, Annex II, Labelling and PL	This variation application was submitted in order to change the dose regimen of fulvestrant from 250 mg to 500 mg given with intramuscular injection every 4 weeks, based on data from the CONFIRM study. No clinically relevant differences with respect to tolerability and toxicity has been demonstrated comparing the 500 mg and the 250 mg doses, but the higher dose was associated with prolonged time to tumour progression or death (HR: 0.8, P = 0.006) and a trend for better overall survival. Consequent changes in the SPC and PL were proposed including posology and method of administration, revised safety and efficacy data based on the CONFIRM study and revised absorption data based on the 500 mg dose. Additional revisions include an updated section 4.6 of the SPC recommending discontinuation of breast-feeding during fulvestrant treatment. The variation also addresses changes on the instructions for administration in the SPC and PL. Minor clarifications and corrections of typographical errors in the product labelling are also included. Furthermore Annex II has been updated in order to include the version numbers for the Pharmacovigilance System and the Risk Management Plan.
R/0014	Renewal of the marketing authorisation.	23/10/2008	16/12/2008	SmPC, Annex II, Labelling and PL	

IA/0016	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	23/09/2008	n/a		
IA/0015	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	23/09/2008	n/a		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2008	n/a	PL	
IB/0011	IB_37_b_Change in the specification of the finished product - add. of new test parameter	22/11/2007	n/a		
IB/0009	IB_27_b_Change to test proc. of immediate packaging - other changes (incl. replacement/addition)	22/11/2007	n/a		
IA/0012	IA_09_Deletion of manufacturing site	17/10/2007	n/a		
IA/0010	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	17/10/2007	n/a		
II/0008	Update of SPC Update of Summary of Product Characteristics	21/09/2006	20/10/2006	SmPC	The MAH applied for a type II variation, upon request by CHMP, to revise sections 4.2 and 5.2 of the SPC following assessment of study 9238IL/0063 on hepatic impairment. The pharmacokinetics of fulvestrant has been evaluated in study 9238IL/0063, a single-dose clinical trial conducted in subjects with Child-Pugh category A and B hepatic impairment due to cirrhosis. A high dose of a shorter duration intramuscular injection formulation was used. There was up to about 2.5-fold increase in AUC in subjects

					with hepatic impairment compared to healthy subjects. In patients administered Faslodex, an increase in exposure of this magnitude is expected to be well tolerated. Child-Pugh category C subjects were not evaluated. No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, Faslodex should be used with caution in these patients. There are no data in patients with severe hepatic impairment.
IB/0006	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	16/02/2006	n/a		
IB/0005	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	16/02/2006	n/a		
IA/0007	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	27/01/2006	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2005	n/a	Labelling and PL	
II/0003	Update of or change(s) to the pharmaceutical documentation	26/05/2005	05/07/2005	SmPC	
II/0002	Update of Summary of Product Characteristics and Package Leaflet	26/05/2005	05/07/2005	SmPC and PL	The MAH applied to update the SPC in section 4.5 following the results of an in vitro study on P450 inhibion and to include "elevated liver enzymes" in section 4.8. The PL has been amended accordingly and in addition, changes to the adresses of local representatives have been implemented.

N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2004	n/a	PL	